

Appl. No. : 10/070,938
Filed : June 4, 2002

REMARKS

In the Office Action, the Examiner maintained the rejection of the pending claims as obvious under 35 U.S.C. § 103 over Naughton, et al. (U.S. Patent No. 5,863,531) in view of Vyakarnam, et al. (U.S. Patent No. 6,534,084) taken with Hinsch, et al. (EP 0 274 898) and Morita (Japanese Patent No. 3-23864).

By this amendment, Claims 1-6 and 12-14 have been cancelled. Claim 7 has been amended to more clearly define the present invention. Support for amended Claim 7 may be found at page 3, line 21 – page 4, line 7; page 6, lines 4-8; and Example 1. Furthermore, Claims 15-19 have been added. Support for new Claims 15-19 may be found at page 4, line 8 – page 5, line 11; page 6, line 9 - page 7, line 12; and in originally-filed Claims 2-6. No new matter has been added thereby. Thus, Claims 7-11 and 15-19 are currently pending in the application. The Examiner's rejections are traversed below.

Rejection under 35 U.S.C. § 103

The Examiner has maintained his previous rejection of all of the pending claims under 35 U.S.C. § 103(a) as being unpatentable over Naughton, et al. (U.S. Patent No. 5,863,531) in view of Vyakarnam, et al. (U.S. Patent No. 6,534,084) taken with Hinsch, et al. (EP 0 274 898) and Morita (Japanese Patent No. 3-23864). The Examiner has repeated the grounds for rejection from the first Office Action and has indicated that Vyakarnam's disclosure of a foam reinforced with fibers shows a motivation to combine Naughton and Vyakarnam with Hinsch and Morita.

The Examiner's rejection rests on two central propositions. First, the Examiner indicates that "the invention of claims 1-6 does not require tissue to be present, and the matrix can be implanting without seeding with cells and culturing to produce tissue." Office Action at 5. In response, Applicant has amended the claims to require that cells be seeded onto the matrix and completely cover it prior to embedding the matrix in vivo. Second, the Examiner concludes that one of skill in the art would have understood from the cited references that reinforcement would be important even if tissue were grown on the matrix before it was implanted. Specifically, the Examiner states that

since the foam of Vyakarnam et al, which is used for tissue engineering can be reinforced with fibers, it would have been apparent that reinforcement is

important irrespective of whether tissue is produced on the foam or sponge before implanting. Even after tissue is engineered on the foam or sponge, it is implanted and reinforcement would have been expected to be important for the same type of reasons as when tissue is not produced on the foam or sponge before an implanting.

Id.

With respect to this second proposition, Applicant respectfully submits that, upon closer consideration, the references cited by the Examiner teach away from the claimed combination. In brief, Vyakarnam discloses the use of reinforcing fibers only in foam used to regenerate bone or cartilaginous tissue attached to bone, where greater stiffness is required. Applicant submits that the Examiner has failed to show compatibility between bone or cartilaginous tissue and cardiovascular tissue. Vyakarnam's disclosure of tissue scaffoldings used in vascular repair does not include the use of reinforcing fibers. Naughton specifically criticizes the use of artificial reinforcing materials in blood vessels, where elasticity is required. Applicant respectfully submits that the Examiner has failed to consider this teaching-away disclosure. Neither Hinsch nor Morita contemplate tissue engineering in which cells are grown in the foam before implantation in the body, and therefore they only suggest that an open-cell foam having no natural tissue therein, which might be expected to be weaker than the surrounding tissue, should be reinforced with fibers before implantation. Applicant submits that one of ordinary skill in the art would not culture cells on the foam or sponge before implanting unless absolutely required to do so, because it is extremely burdensome to culture cells in this manner. Furthermore, Morita makes clear that the presence of such fibers is only required until the tissue is regenerated. Applicant notes that the tissue-covered matrix is reinforced in the pending claims. Considering the disclosure of the references as a whole, Applicant submits that one of skill in the art reading these references would be discouraged from placing reinforcing fibers in a matrix used for generating cardiovascular tissue via in vitro tissue culture followed by in vivo transplantation. The cited references at least provide no motivation for doing so. The results obtained in Example 1 were therefore surprising and non-obvious.

The disclosure of each reference will be discussed in detail below.

Vyakarnam '084

As the Examiner indicates, Vyakarnam discloses foam structures that can be composed of copolymers of lactide and which can be used to regenerate tissue such as vascular grafts. Furthermore, as the Examiner notes, Vyakarnam teaches that the foam may be reinforced with fibers. Specifically, the discussion of fibers to which the Examiner refers is within a section of the Vyakarnam specification discussing cartilage. Here, however, the reinforcing fibers are restricted to a section of the cartilage that attaches to bone, in which sufficient stiffness is required:

[A]t the bottom of this structure there is a need for larger pores (about 150 μm to about 300 μm) with higher stiffness to be structurally compatible with cancellous bone. The foam in this section could be reinforced with ceramic particles or fibers made up of calcium phosphates and the like.

Vyakarnam '084 at col. 6, lines 36-41 (emphasis added). Furthermore, Vyakarnam also discusses the use of fibers in tissue scaffoldings for bone repair, which would clearly also require significant stiffness. Vyakarnam '084 at col. 8, lines 5-12. But although Vyakarnam specifically describes possible tissue scaffoldings for use in skin and vascular repair, the reference does not disclose the use of artificial reinforcing fibers in such applications. By inference, Vyakarnam suggests to one of skill in the art that the use of reinforcing fibers is only preferable where higher stiffness is required, such as in those parts of cartilage which are connected to bone or in bone itself.

This understanding of Vyakarnam is reinforced by the discussion of Hinsch '898 therein. Vyakarnam discusses Hinsch in the "Background of the Invention" section, specifically noting that Hinsch teaches the reinforcement, with fibers or the like, of a porous open cell foam. Vyakarnam '084 at col. 1, lines 36-41. However, Vyakarnam then specifically criticizes Hinsch as deficient. Vyakarnam '084 at col. 1, lines 48-49.

Naughton '531

As the Examiner indicates, Naughton discloses foam structures that may be used in regenerating vasculature. However, Naughton does not teach the use of fibrous reinforcing materials such as those of the present application. In fact, Naughton specifically criticizes the use in the prior art of artificial materials to provide "the strength and elasticity required of blood vessels in vivo," and notes that the criticized prior art technique resulted in a construction that

“completely lacked elastin.” Naughton ‘531 at col. 4, lines 2-6. The presence of elastin “gives arteries the ability to stretch with every contraction of the heart.” Naughton ‘531 at col. 24, lines 48-50. Naughton therefore indicates that when natural components such as elastin are present in tubular biological replacement tissues grown on an unreinforced matrix, they may be used as replacement tissues in the body:

The different biological structures described below have several features in common. They are all tubular structures primarily composed of layers of stromal tissue with an interior lining of epithelium (gastrointestinal and genitourinary) or endothelium (blood vessels). Their connective tissues also contain layers of smooth muscle with varying degrees of elastic fibers, both of which are especially prominent in arterial blood vessels. By including and sustaining these components in three-dimensional cultures according to the present invention, the tissues they compose can attain the special structural and functional properties they require for proper physiological functioning in vivo. They can then serve as replacements for damaged or diseased tubular tissues in a living body.

Naughton ‘531 at col. 22, lines 49-62. Naughton would accordingly suggest two things to one of skill in the art. One is that the replacement tissues grown on the disclosed unreinforced matrices or foams have sufficient strength to be implanted in the body as prosthetic cardiovascular tissue once the tissue culture is complete. The other is that it is not advisable to employ artificial reinforcing materials to supply the strength and elasticity necessary for blood vessels in vivo, as this may hinder the development of the cellular and extracellular components required for the regenerated blood vessels to properly function.

Hinsch ‘898

Hinsch discloses an implant made of a resorbable polyester such as polylactide or the like that has pores with an average pore diameter of 10-200 μm and has a textile reinforcement formed of resorbable plastic embedded therein. Hinsch does not teach or suggest that cells may be grown by being seeded on the implant prior to implantation. Rather, the Hinsch implant is designed to be implanted and then colonized by the surrounding tissue. In other words, Hinsch describes the problem solved by the invention as the need for an implant “which, despite the adequately open-cell structure to permit the growing-in of cells and blood vessels, ha[s] an adequate strength and particularly tensile strength.” Hinsch ‘898 at p. 2, lines 51-53 (emphasis added). Hinsch does not suggest that cells can be seeded on the implant ex vivo. Accordingly,

Appl. No. : 10/070,938
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one of skill in the art would understand from Hinsch that reinforcement of an open-cell foam implant may be necessary when cells are not seeded onto the implant prior to implantation in vivo.

Morita '864

An English-language translation of the Morita specification and claims is attached. As the Examiner notes, Morita discloses a filler material for use in vivo that uses poly-L-lactic acid. Like Hinsch, Morita does not disclose seeding and growing cells on the filler material prior to implantation. Neither does Morita disclose that the filler material is used for regenerating blood vessels or similar cardiovascular tissue structures.

Furthermore, Morita clearly indicates that reinforcement is not necessary when fully regenerated tissue is present. Specifically, the implant disclosed in Morita is said to “maintain[] its strength and shape over a long period of time until the regeneration of the tissue.” Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). One of skill in the art would accordingly understand from Morita that if tissue was generated ex vivo by tissue engineering techniques, artificial reinforcement of the implant would not be necessary.

Applicant submits that the combined teachings of these references would counsel one of skill in the art to avoid the use of artificial reinforcements in cardiovascular tissue engineered ex vivo. Vyakarnam's awareness of the possibility of using reinforcing fibers, and his choice to employ such fibers only where greater stiffness is required (as opposed to the elasticity required of blood vessels), together with Naughton's criticism of the use of artificial reinforcements in blood vessel prostheses, would indicate to one of skill in the art that use of reinforcing fibers was at best unnecessary, and probably unwise, as it might make the resulting prostheses too stiff or hinder the development of the natural components that provide elasticity. Both Hinsch and Morita indicate that the purpose of reinforcing fibers is simply to provide the mechanical strength which is lacking in an uncultured open-cell structure which is implanted into the body. See Hinsch '898 at page 2, lines 51-53 and page 3, lines 8-11; Morita translation at page 5, lines 13-14 (Morita '864 at page 7, lines 5-7). Indeed, Morita suggests that the fibers are only required when the tissue is not yet fully regenerated. Thus, these disclosures support the view that the reinforcing fibers are only necessary in a matrix for culturing cardiovascular tissue when the

Appl. No. : 10/070,938
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matrix has not yet been cultured with cells, and that when such cells are present on the matrix, they would provide sufficient strength for the prosthetic tissue in vivo.

In view of these combined teachings, as described above, Applicant submits that one of skill in the art would have concluded that it was inadvisable, and at least unnecessary, to place artificial reinforcing fibers into a matrix seeded with cardiovascular cells to regenerate a blood vessel before implantation, as the presence of the fibers could make the prosthesis too stiff or impede the development of the cardiovascular tissue. Accordingly, the results obtained by the present invention, as shown in Example 1, are surprising and the invention is not obvious over the combination of cited references.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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